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Darbepoetin alfa administration in patients with non-Hodgkin lymphoma and chemotherapy-induced anemia receiving (\pm R)CHOP

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Abstract: IMPACT NHL was a multicenter, observational study in adults with non-Hodgkin lymphoma receiving CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy with or without rituximab. Erythropoietin-stimulating agent treatment was given according to routine clinical practice and physician preference. In a subanalysis, outcomes were evaluated in 207 patients who received darbepoetin alfa (DA). The most common reason (81%) for initiating DA was low/declining hemoglobin (Hb) concentration. Mean (\pm standard deviation) duration of DA exposure was 8.8 ± 6.9 weeks (mean number of doses, 5.1 ± 4.6). Overall, 23% of patients had chemotherapy and DA treatment synchronized more than 75% of the time. At the time of DA initiation, 67% of patients had Hb concentrations in the guideline-recommended range (9-11 g/dl). Of 89 patients with Hb concentrations <10 g/dl at DA initiation and still receiving DA 5 weeks later, 92% (Kaplan-Meier) achieved Hb concentrations 10-12 g/dl between week 5 and at the end of treatment.

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**DARBEPOETIN ALFA ADMINISTRATION IN PATIENTS WITH
NON-HODGKIN LYMPHOMA AND CHEMOTHERAPY-INDUCED
ANEMIA RECEIVING (±R)CHOP**

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Abstract

IMPACT NHL was a multicenter, observational study in adults with non-Hodgkin lymphoma receiving CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy with or without rituximab. Erythropoietin-stimulating agent treatment was given according to routine clinical practice and physician preference. In a subanalysis, outcomes were evaluated in 207 patients who received darbepoetin alfa (DA). The most common reason (81%) for initiating DA was low/declining hemoglobin (Hb) concentration. Mean (\pm standard deviation) duration of DA exposure was 8.8 ± 6.9 weeks (mean number of doses, 5.1 ± 4.6). Overall, 23% of patients had chemotherapy and DA treatment synchronized more than 75% of the time. At the time of DA initiation, 67% of patients had Hb concentrations in the guideline-recommended range (9–11 g/dL). Of 89 patients with Hb concentrations <10 g/dL at DA initiation and still receiving DA 5 weeks later, 92% (Kaplan–Meier) achieved Hb concentrations 10–12 g/dL between week 5 and end of treatment.

Keywords: anemia, chemotherapy, darbepoetin alfa, erythropoietin-stimulating agents, non-Hodgkin lymphoma

Introduction

Hemoglobin (Hb) concentrations <8 g/dL have been reported in 13–25% of patients receiving CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy, with or without rituximab, every 14 ([±R]CHOP-14) or 21 days ([±R]CHOP-21) [1–3]. Current treatment guidelines – such as those of the European Organisation for Research and Treatment of Cancer (EORTC) [4,5] – state that treatment with an erythropoietin-stimulating agent (ESA) may be initiated when Hb concentrations fall to 9–11 g/dL in patients displaying anemia-related symptoms; the aim of ESA treatment is to restore the Hb concentration to a level no greater than 12 g/dL.

Methods

IMPACT NHL was a multicenter, observational study of neutropenia prophylaxis and management [6], and anemia management, in adult patients with non-Hodgkin lymphoma receiving (±R)CHOP chemotherapy. Anemia-related outcomes in patients receiving any ESA have been reported previously [7]. Overall, 22% of patients received an ESA, of whom 51% received darbepoetin alfa (DA), compared with 48% who received epoetin. DA has a serum half-life that makes less-frequent administration possible [8], and the dosing recommendations differ from those of epoetin-alfa and -beta in their respective Summaries of Product Characteristics. Therefore, data from IMPACT NHL for those patients who received DA were analyzed separately.

IMPACT NHL was conducted in 14 European countries and Australia (www.clinicaltrials.gov: NCT00903812). Patients who had received (±R)CHOP-14 or (±R)CHOP-21 could be enrolled retrospectively (5–10 patients per center) or prospectively (10–12 patients per center). The end of the observational period was defined as the date the

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patient completed planned chemotherapy or the date when chemotherapy was stopped.

Details of the study design have been presented previously [6].

ESA treatment was given according to routine clinical practice and physician preference.

Patients could switch to a different ESA at any time, but were categorized for analysis according to the first ESA they received, with data after the switch excluded from the analysis. The present analysis included patients who received DA (either every 7 days or 21 days) as their first ESA.

Patients were adults (age ≥ 18 years) diagnosed with any histologic type of NHL. All patients were planned to receive at least three 14- or 21-day cycles of (\pm R)CHOP. For patients enrolled retrospectively, eligibility was assessed on the profile at the time treatment was planned, not on outcome or number of delivered cycles.

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by ethics committees and institutional review boards at all participating centers.

Written informed consent was obtained from all patients where required.

The full analysis set (FAS) included all patients who started at least one cycle of (\pm R)CHOP and provided data. Anemia-related outcomes included ESA exposure and change in Hb concentration after receiving ESA treatment. In addition, requirement for blood transfusion was evaluated in a subset of patients who were enrolled in the study for at least 29 days (including the day of ESA initiation) after starting ESA treatment.

The statistical analysis was descriptive in nature. Categorical data were summarized by the number and percentage of patients in each category, with summary statistics generated for continuous data. For patients who received one or more transfusions, data on Hb concentrations were disregarded for 28 days post-transfusion.

Results

Of 1829 patients in the FAS, 404 (22%) received an ESA, of whom approximately half ($n=207$) received DA and formed the population for this analysis. Of the 207 patients who received DA, 32 (15%) were also participating in another clinical trial. Baseline characteristics have been reported previously [7]. In brief, mean (\pm standard deviation [SD]) age was 63.8 ± 12.8 years and 52% of patients were female. Most patients had diffuse large B-cell lymphomas (68%) and Eastern Cooperative Oncology Group performance statuses of 0–2 (91%). Ann Arbor stage was I–III in 43% of patients and IV in 57%. Almost all patients (96%) had no bone marrow involvement. Most patients (67%) received R-CHOP-21, with 27% receiving R-CHOP-14, 4% receiving CHOP-21, and 2% receiving CHOP-14. Most patients (77%) received six or eight cycles of chemotherapy.

For most patients, the reason for initiating DA, as specified by the treating physician (more than one reason could be specified), was a low or declining Hb concentration ($n=167$; 81%) and/or to reduce the risk of chemotherapy-induced anemia ($n=45$; 22%). Other reasons included evidence-based guidelines ($n=7$; 3%) and other anemia-related symptoms ($n=1$; 0.5%). The mean (\pm SD) duration of DA exposure was 8.8 ± 6.9 weeks and the mean number of doses was 5.1 ± 4.6 . Patients made an average of six clinic visits per month, of which two visits, on average, were for DA treatment only (Table 1). Overall, 48 patients (23%) had chemotherapy and DA treatment synchronized more than 75% of the time.

Table 1. Clinic visits and DA synchronization with chemotherapy

	Patients receiving DA (<i>n</i>=207)
No. clinic visits per month	
Mean±SD	6.0±4.1
Range	1–19
No. clinic visits for DA alone	
Mean±SD	1.8±2.9
<i>n</i> (%)	
0	95 (46)
1–2	65 (31)
3–9	39 (19)
≥10	8 (4)
Percentage of DA administrations synchronized with chemotherapy visits, <i>n</i> (%)	
100%	40 (19)
75 to <100%	8 (4)
50 to <75%	11 (5)
25 to <50%	26 (13)
>0 to <25%	92 (44)
0	30 (14)

DA, darbepoetin alfa; SD, standard deviation

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At the time of DA initiation, mean (\pm SD) Hb concentration in 201 patients for whom data were available was 10.1 ± 1.3 g/dL (range 5.9–13.7 g/dL). Of these, most ($n=139$; 67%) had Hb concentrations of 9–11 g/dL at the time of initiation, with 29 patients (14%) and 33 patients (16%) having Hb concentrations <9 or >11 g/dL, respectively. Of the 89 patients with Hb concentrations <10 g/dL at DA initiation and still receiving DA treatment at 5 weeks after initiation, 38 (crude percentage, 43%; Kaplan–Meier percentage, 92% [95% confidence interval [CI]: 78–105%]) achieved Hb concentrations 10–12 g/dL between week 5 after DA initiation and the end of the treatment period (Table 2). Overall, 27% of patients receiving DA experienced an excess rate of rise, defined as a change in Hb concentration ≥ 1.0 g/dL in 14 days, ≥ 1.5 g/dL in 21 days, or ≥ 2.0 g/dL in 28 days.

Between DA initiation and end of treatment, 57 patients (crude percentage, 28%; Kaplan–Meier percentage, 33% [95% CI: 25–41%]) required a red-blood-cell transfusion, with 33% of all transfusions given in the first 2 weeks after DA initiation. Of the 57 patients who required a transfusion, 3 (5%) required 1 unit, 23 (40%) required 2–3 units, 15 (26%) required 4–5 units, and 16 (28%) required ≥ 6 units. Overall, the mean (\pm SD) number of units was 4.2 ± 2.8 . The most common Hb ranges at the time of transfusion were 9– <10 g/dL ($n=19$; 33%) and 10– <11 g/dL ($n=15$; 26%). The transfusion subset (ie patients who spent ≥ 29 days in the study after initiating ESA treatment) included 176 patients, of whom 31 (crude percentage, 18%; Kaplan–Meier percentage, 29% [95% CI: 17–41%]) required a transfusion between week 5 after DA initiation and end of treatment.

Table 2. Achievement of specified Hb concentrations from 5 weeks after initiation of DA treatment to end of the DA treatment period*

<i>Patients with Hb <10 g/dL at ESA initiation and who remained in study at week 5 (n=89)</i>	
Achieved Hb ≥10 g/dL	
<i>n</i>	46
Crude percentage	52
KM percentage [†] (95% CI)	95 (87–103)
Achieved Hb 10–12 g/dL	
<i>n</i>	38
Crude percentage	43
KM percentage [†] (95% CI)	92 (78–105)
<i>Patients with Hb <11 g/dL at ESA initiation and who remained in study at week 5 (n=155)</i>	
Achieved Hb ≥11 g/dL	
<i>n</i>	68
Crude percentage	44
KM percentage [†] (95% CI)	88 (74–101)
<i>Patients with Hb <12 g/dL at ESA initiation and who remained in study at week 5 (n=182)</i>	
Achieved Hb ≥12 g/dL	
<i>n</i>	48
Crude percentage	26
KM percentage [†] (95% CI)	62 (41–82)
Achieved Hb 12–13 g/dL	
<i>n</i>	35
Crude percentage	19
KM percentage [†] (95% CI)	42 (26–59)

CI, confidence interval; KM, Kaplan–Meier

Hb values within 28 days after red-blood-cell transfusions are excluded

*Defined as date of ending DA treatment +17 days for patients dosed every 7 days and +31 days for patients dosed every 21 days

[†]The Kaplan–Meier percentage accounts for study drop-outs and is, therefore, larger than the crude percentage based on the number of patients in the study at week 5

Discussion

Overall, the results of this observational study show that DA provided good control of Hb concentrations for most patients, with a quarter of patients experiencing an excess rate of Hb rise. Hb concentration at the time of initiation was in the range 9–11 g/dL in 67% of patients, which is consistent with the guidelines of the EORTC at the time of the study [4,5,9]. Thus, one-third of patients started DA at concentrations outside the recommended range, including 14% who initiated DA at concentrations below 9 g/dL.

The summaries of Hb concentration at DA initiation in this analysis were based on all patients within the DA-treated set and cannot, therefore, be compared directly with the published data for the ESA-treated study population, for which percentages were based on the number of patients with available Hb results. The results of patients receiving DA did, however, appear broadly similar to those of patients receiving other ESAs in the overall study population, in which 65% of patients had Hb concentrations of 9–11 g/dL when ESA treatment was initiated, and where 89% (95% CI: 78–101; Kaplan–Meier percentage) of patients achieved Hb concentrations 10–12 g/dL between week 5 and the end of the treatment period [7]. The results of the present analysis are also consistent with older observational studies of ESA treatment [10,11]. As IMPACT NHL was an observational study, and included patients enrolled retrospectively, the results should be interpreted with the appropriate caution.

One issue that deserves consideration in the light of our data, in which some patients experienced Hb overshoot and others began DA treatment at a non-indicated baseline Hb level, is the potential for excess disease progression and/or mortality, as raised in previous publications [12,13]. More recent studies, however, contradict this hypothesis. For example, in a pooled analysis of randomized, double-blind, placebo-controlled trials in patients with

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chemotherapy-induced anemia receiving DA or placebo (n=2122), DA had no impact on mortality, progression-free survival or disease progression [14]. Similarly, three meta-analyses – one of studies in patients with lymphoproliferative malignancies [15], one in patients with lung cancer [16] and one broader analysis of oncology studies [17] – found no effect of ESAs on survival or disease progression.

In conclusion, this observational study found that DA was initiated most frequently in response to low or declining Hb concentrations. Hb concentration at the time of initiation was consistent with current EORTC guidelines in two-thirds of patients. Most patients who had Hb <10 g/dL when DA was initiated achieved stable target Hb concentrations of 10–12 g/dL by the end of the treatment period. Overall, we believe that the results of this analysis provide useful information for clinicians considering DA treatment for those patients with NHL who are receiving chemotherapy and have developed anemia.

References

1. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, *et al.* CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002;346:235–42.
2. Delarue R, Tilly H, Salles G, Gisselbrecht C, Mounier N, Fournier M, *et al.* R-CHOP14 compared to R-CHOP21 in elderly patients with diffuse large B-cell lymphoma: results of the interim analysis of the LNH03-6B GELA study. *Blood (ASH Annual Meeting Abstracts)* 2009;114:406.
3. Pfreundschuh M, Trümper L, Kloess M, Schmits R, Feller AC, Rübke C, *et al.* Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of

elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood 2004;104:634–41.

4. Bokemeyer C, Aapro MS, Courdi A, Foubert J, Link H, Osterborg A, *et al.* EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. Eur J Cancer 2007;43:258–70.
5. Aapro MS, Link H. September 2007 update on EORTC guidelines and anemia management with erythropoiesis-stimulating agents. Oncologist 2008;13 (Suppl 3):33–6.
6. Salar A, Haioun C, Rossi FG, Pettengell R, Johnsen HE, Jaeger U, *et al.* Febrile neutropenia risk assessment and granulocyte-colony stimulating factor support in patients with diffuse large B cell lymphoma receiving R-CHOP regimens. Blood (ASH Annual Meeting Abstracts) 2009;114:107.
7. Haioun C, Salar A, Pettengell R, Johnsen HE, Duehrsen U, Rossi FG, *et al.* Anemia and erythropoiesis-stimulating agent administration in patients with non-Hodgkin lymphoma treated with cyclophosphamide, doxorubicin, vincristine, and prednisolone +/- rituximab chemotherapy: results from an observational study. Leuk Lymphoma 2011;52:796–803.
8. Amgen Ltd. Aranesp PFS. Breda: Amgen Europe BV, 2011.
9. Bokemeyer C, Aapro MS, Courdi A, Foubert J, Link H, Osterborg A, *et al.* EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer. Eur J Cancer 2004;40:2201–16.
10. Mark TL, McKenzie RS, Fastenau J, Piech CT. Retrospective observational study of patients with chemotherapy-related anemia receiving erythropoietic agents. Curr Med Res Opin 2005;21:1347–54.

11. Pujade-Lauraine E, Richard AJ, Sapède C, Hayward C. Erythropoietic agents in anaemic patients with cancer: a retrospective observational survey of epoetin alpha, epoetin beta and darbepoetin alpha use in routine clinical practice. *Oncol Rep* 2005;14:1037–44.
12. Tonelli M, Hemmelgarn B, Reiman T, Manns B, Reaume MN, Lloyd A, et al. Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. *CMAJ* 2009;180:E62–71.
13. Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. *Lancet* 2009;373:1532–42.
14. Ludwig H, Crawford J, Osterborg A, Vansteenkiste J, Henry DH, Fleishman A, *et al.* Pooled analysis of individual patient-level data from all randomized, double-blind, placebo-controlled trials of darbepoetin alfa in the treatment of patients with chemotherapy-induced anemia. *J Clin Oncol* 2009;27:2838–47.
15. Hedenus M, Osterborg A, Tomita D, Bohac C, Coiffier B. Effects of erythropoiesis-stimulating agents on survival and other outcomes in patients with lymphoproliferative malignancies: a study-level meta-analysis. *Leuk Lymphoma* 2012; Epub ahead of print.
16. Vansteenkiste J, Glaspy J, Henry D, Ludwig H, Pirker R, Tomita D, et al. Benefits and risks of using erythropoiesis-stimulating agents (ESAs) in lung cancer patients: Study-level and patient-level meta-analyses. *Lung Cancer* 2012;76:478–85.
17. Glaspy J, Crawford J, Vansteenkiste J, Henry D, Rao S, Bowers P, et al. Erythropoiesis-stimulating agents in oncology: a study-level meta-analysis of survival and other safety outcomes. *Br J Cancer* 2010;102:301–15.

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Potential conflicts of interests

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